



Inducible protein-10 as a predictive marker of antiviral hepatitis C treatment

A systematic review

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Inducible protein-10 as a predictive marker of antiviral hepatitis C treatment: A systematic review

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Data sharing statement: The technical appendix, and dataset are available from the corresponding author at nina.weis@regionh.dk.

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Abstract

AIM

To investigate interferon- γ -inducible protein-10's (IP-10) potential to anticipate rapid (RVR)- and sustained virological responses (SVR) to chronic hepatitis C (CHC) treatment.

METHODS

We included case series examining RVR or SVR in relation to 24 or 48 wk treatment for CHC, in patients treatment free for at least six months, with genotype 1 or 4, and in relation to 24 wk treatment for genotype 2 and 3, with pegylated interferon in combination with ribavirin. Patients had to have both a baseline IP-10 level as well as a hepatitis C virus (HCV)-RNA determination 4 wk after treatment initiation or 24 wk after end of treatment. Studies including patients with liver diseases other than CHC, human immunodeficiency virus-infection, treatment with immunosuppressants or cytostatics, alcohol dependency or active intravenous drug-use were excluded. We found 81 articles by searching the MEDLINE and EMBASE databases. Eight studies were eligible for inclusion. Their quality were assessed using an 18 point checklist for case series, developed using a modified Delphi technique. Information was extracted from the articles, and no raw data was requisitioned. The review protocol was

registered at the International Prospective Register of Systematic Reviews (reg. number: CRD42014008736).

RESULTS

Three studies reported on baseline IP-10 level in association with RVR. A significant association was found for HCV genotype 1 infection by two studies. Only two studies reported on HCV genotype 4 infected and genotype 2 and 3 infected patients, respectively. A trend was seen for an association between RVR and baseline IP-10 for genotype 4, while no association was found for genotype 2 and 3. Seven studies provided information regarding baseline IP-10 and SVR. Following the pattern regarding rapid virological response all five studies examining SVR in relation to baseline IP-10 levels for HCV, genotype 1 infected patients showed a significant association. Likewise a significant association was seen for HCV, genotype 4 infected, while no association was found for HCV, genotype 2 and 3 infected. Though only two studies examined the association for HCV genotype 4 infected and HCV genotype 2 and 3 infected respectively.

CONCLUSION

We found indications of a possible association between baseline IP-10 level and virological responses in patients with CHC genotype 1 and 4.

Key words: Chronic hepatitis C; Inducible protein-10's; Sustained virological response; Interferon- γ -inducible protein-10; CXCL-10; Chemokine; Genotype; Pegylated interferon; Ribavirin; Rapid virological response

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Core tip: This is the first systematic review examining the association between baseline levels of interferon- γ -inducible protein-10 (IP-10) and virological response to treatment with pegylated interferon and ribavirin among patients chronically infected with hepatitis C virus, genotype 1-4. We found a possible correlation for genotype 1 and 4 infected patients, indicating that baseline IP-10 levels could predict which patients, infected with genotype 1 or 4, would have the highest likelihood of benefitting from antiviral treatment with pegylated interferon and ribavirin. These findings can be especially relevant in countries, where treatments with direct acting antivirals are not readily applicable.

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INTRODUCTION

Every year 3-4 million individuals are infected with hepatitis C virus (HCV) of whom only 20%-35% clear the

infection, meaning that 2.4-3.2 million individuals remain chronically infected, defined as detectable HCV-RNA in two consecutive measurements \geq six months apart. Globally, the prevalence of chronic hepatitis C (CHC) is estimated to 150 million people, with CHC being the leading cause of chronic liver disease^[1]. CHC can lead to formation of connective tissue (fibrosis) in the liver. However, the rate and severity of the inflammation and fibrosis vary^[2,3]. Though only 5%-20% of HCV infected patients develop cirrhosis, these patients have an increased risk of developing hepatocellular carcinoma, a condition responsible for more than 300000 deaths annually^[1].

Until recently, the standard of care for CHC was lengthy dual therapy with pegylated interferon plus ribavirin (peg-IFN/RBV), either as 180 μ g peg-IFN- α -2a weekly or peg-IFN- α -2b 1.5 μ g/kg per week in combination with ribavirin 15 mg/kg per day (minimum 1000 mg daily and maximum 1400 mg daily), fixed doses of 1000 mg for patients < 75 kg and 1200 mg for patients > 75 kg with genotype 1 or 4 or flat dosing of 800 mg daily for genotypes 2 and 3 - a treatment with modest success rates, severe adverse events and variation in treatment response between genotypes^[4]. Therefore, a great effort has been put into identifying biomarkers to predict rapid virological response (RVR), defined as undetectable serum HCV-RNA at week four of antiviral treatment, and sustained virological response (SVR), defined as the undetectable HCV-RNA 24 wk after discontinuing antiviral treatment. One of the most promising chemokine biomarker candidate is interferon- γ inducible protein-10 (IP-10). Both intrahepatic IP-10 mRNA and plasma levels of IP-10 are elevated in individuals with CHC^[5,6], strongly indicating that intrahepatic IP-10 is the source of plasma IP-10. Several studies have suggested that pretreatment levels of IP-10 have the capability to predict RVR and SVR^[6-9]. In addition, hepatic inflammation and fibrosis have been shown to correlate with IP-10 levels^[10-12], and it has been proposed, that plasma levels of IP-10 can predict the risk of fibrosis progression^[13]. Later years have seen the forthcoming of the new direct acting antivirals (DAA), and all current treatment recommendations for CHC patients from the European Association for the Study of the Liver contain at least one DAA^[14]. The current DAAs are the NS5B polymerase inhibitor, sofosbuvir, the NS3/4A protease inhibitor simeprevir and the NS5A-replication-inhibitors daclatasvir and ledipasvir or the so-called 3D regimen containing the dual NS3/4A protease inhibitors Paritaprevir/Ritonavir, the NS5A inhibitor Ombitasvir and the NS5B palm polymerase inhibitor Dasabuvir. This has yielded the possibility for treating CHC patients with interferon free, all-oral regimens, with high SVR-rates and fewer adverse events^[14-18]. Despite of these great advantages, the cost of DAAs will without doubt substantially delay their introduction as standard treatment in low and middle-income countries by years to come. Moreover, even in high income countries, treatment with DAA therapy is reserved for patients with advanced liver disease, despite the fact that a majority of patients are expected to benefit from the treatment. Therefore,

peg-IFN/RBV treatment still has a role to play in treatment of patients with CHC, and the need for markers that can predict successful treatment outcomes to peg-INF- α /RBV are still needed.

Several studies have independently shown an association between virological response and baseline IP-10 concentrations for CHC patients infected with genotype 1 and 4^[19-21]. However, the association seems to be lacking for CHC patients, infected with HCV genotype 2 and 3^[21,22]. Despite this being the case, a systematic review to address and clarify the differences in IP-10 properties, in relation to the different HCV genotypes, is missing. The aim of this systematic review was therefore to examine IP-10's ability to predict RVR and SVR in patients with CHC genotypes 1-4 treated with peg-IFN/RBV. We succeeded in doing so, with data presented in the following.

MATERIALS AND METHODS

On initiation of this review a protocol was made and registered at the International Prospective Register of Systematic Reviews (PROSPERO) - registration number: CRD42014008736. Protocol can be found at <https://www.crd.york.ac.uk/PROSPERO/>.

Literature search

Using the search profiles listed in the Appendix I in the supporting information, suitable literature was identified in MEDLINE and EMBASE. The first article sorting was performed by rating the article headlines, while the second sorting was performed on abstract level. Papers passing both sorting rounds were considered for the review, and thoroughly scrutinized based on pre-defined inclusion and exclusion criteria as listed below. The initial search provided 81 articles; 34 in MEDLINE and 47 in EMBASE. After the first- and second-sorting, 14 articles remained from MEDLINE and 14 articles from EMBASE of which 10 were duplicates. One article was found by manual searching the references, bringing the total number of articles after the third sorting to 19. During the third sorting, 11 articles were excluded^[6,8,22-30]. This left 8 studies for inclusion^[7,9,19,21,31-34]. Overview of the entire sorting process is shown in Figure 1.

Inclusion criteria

Case series examining RVR or SVR in relation to 24 or 48 wk treatment with either 180 μ g Peg-IFN- α -2a weekly or peg-INF- α -2b 1.5 μ g/kg per week in combination with ribavirin 15 mg/kg per day (minimum 1000 mg daily and maximum 1400 mg daily) or fixed doses of 1000 mg for patients < 75 kg and 1200 mg for patients > 75 kg or flat dosing of 800 mg daily, in CHC patients infected with HCV, genotypes 1 or 4, treatment free for at least six months prior to inclusion, with both a baseline IP-10 level- and HCV-RNA determination, as well as a HCV-RNA determination four weeks after treatment initiation to assess RVR and/or 24 wk after end of treatment to assess SVR.

Case series studies examining RVR or SVR, in rela-

tion to 24 wk treatment with either 180 μ g Peg-IFN- α -2a per week or peg-INF- α -2b 1.5 μ g/kg per week in combination with ribavirin 800 mg daily or fixed doses of 1000 mg for patients < 75 kg and 1200 mg for patients > 75 kg, in CHC patients infected with HCV, genotypes 2 or 3, treatment free for at least six months prior to inclusion, with both a baseline IP-10 level- and HCV-RNA determination 4 wk after treatment initiation to assess RVR and/or 24 wk after end of treatment to assess SVR.

Exclusion criteria

Liver diseases other than CHC, Co-infection with human immunodeficiency virus (HIV), co-infection with hepatitis B virus (HBV), alcohol dependency (regular intake of \geq 75 g/d), active intravenous drug-use, treatment with immunosuppressants or cytostatica and prior treatment for CHC within the last 6 mo.

Quality assessment

The quality of the 8 included articles were appraised using an 18 point checklist for case series, developed using a modified Delphi technique^[35]. Each criterion can be answered with "yes", "no" or "partially reported/unclear", with the 18 criteria being weighted equally. In line with a pilot study conducted testing the assessment tool, we choose to rate studies with 14 or more "yes responses" as "high-quality studies", and studies with 13 or less "yes responses" as "low-quality studies". No studies were excluded on the basis of the criteria scores. The full checklist can be found in the Appendix II in the supporting information. Table 1 shows the sum score of the checklist. The baseline demographics regarded as important for the appraisal of the studies were: Number of patients included, patient ethnicity, patient age, male/female ratio, HCV RNA, liver enzyme level [alanine transaminase (ALT) or aspartate transaminase (AST)], body mass index (BMI), genotype, liver fibrosis stage and distribution on interleukin 28B (IL28B) single nucleotide polymorphism (SNPs).

RESULTS

Patient baseline demographic

All information was extracted from the articles, no raw data was requisitioned. Overall, presentation of baseline demographic data was missing in one study. Instead, this study provided baseline demographics in the following subpopulations: IL28 *rs12979860* (CC, CT, TT), *rs12980275* (AA, AG, GG), *rs8099917* (TT, TG, GG)^[34]. Only baseline characteristics for *rs12979860* are reported in the review, as these were representative for the study population. All studies provided baseline information on total number of patients included, gender and age. Four studies failed to provide BMI^[7,9,19,31], and four studies did not supply exact information regarding patient ethnicity^[7,9,19,32]. Information regarding number of patients included, ethnicity, age, male/female ratio, and BMI is reported in Table 2. ALT or AST values were not reported by two studies^[33,34], one of these however stated that all patients included had two

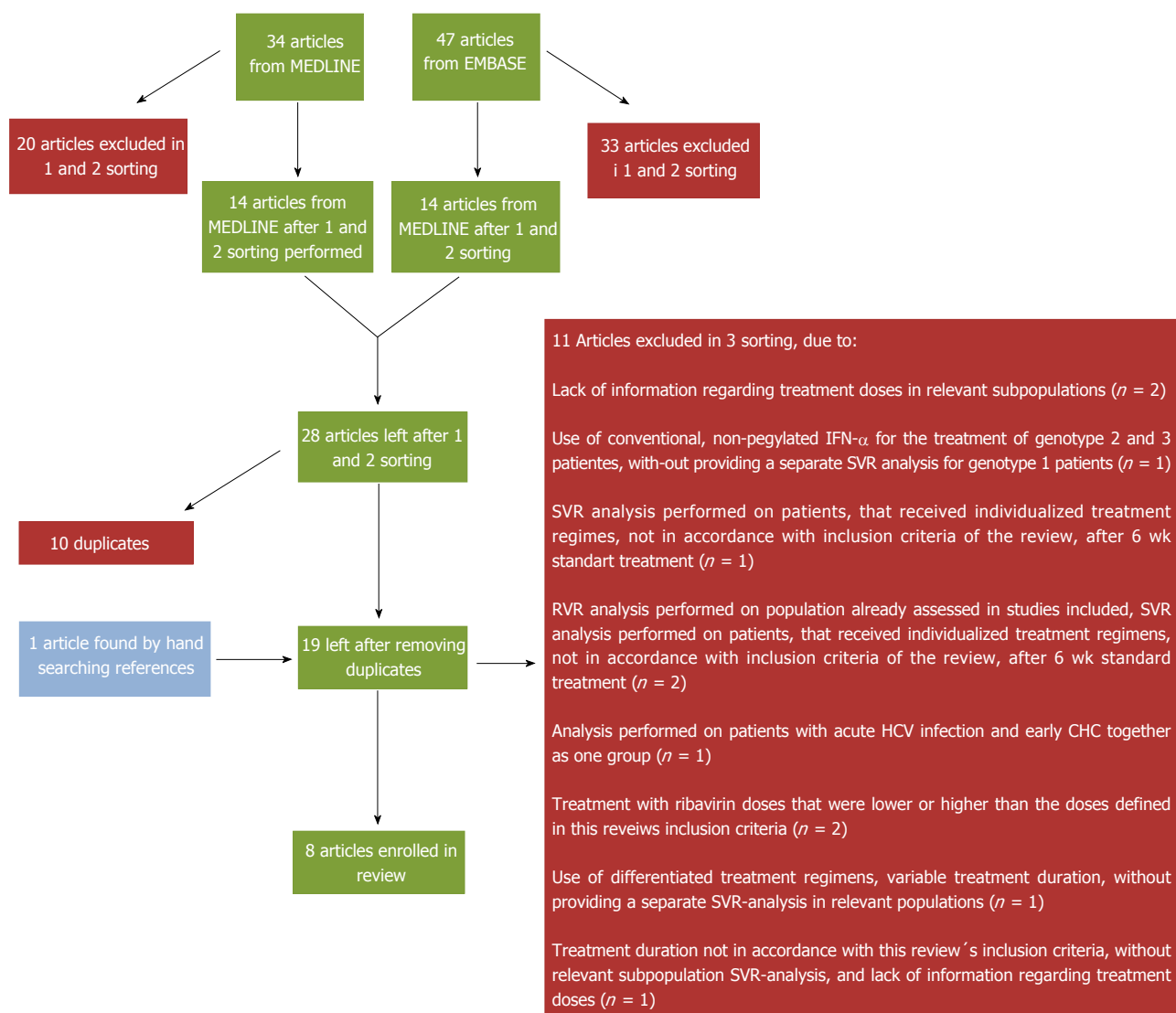


Figure 1 Flow chart depicting the sorting of articles. The chart depicts the number of articles found by searching the MEDLINE and EMBASE databases 04.15.2014, the number of articles excluded during the first and second sorting, the number of duplicates, the number of articles found by manual searching references, and the number of articles excluded in the third sorting, with indication of the reason for exclusion. Articles progressing down the chart from the original search to final inclusion are marked with green boxes, articles found by manual search are marked with blue boxes, and articles excluded are marked with red boxes. SVR: Sustained virological responses; RVR: Rapid virological responses; CHC: Chronic hepatitis C; HCV: Hepatitis C virus.

serum ALT values above the upper limit of normal within 6 mo of treatment initiation^[34]. Effect on liver parenchyma and HCV-RNA load are shown in Table 3. Regarding fibrosis stage, four studies used the Ishak score^[7,31,33,34], two studies used the Scheuer score^[9,32], and two studies used the Metavir staging system^[19,21]. Overview of genotype and fibrosis stage is presented in Table 4. Information regarding treatment regimens can be found in Table 5. Four studies provided information on IL28B SNP distribution. An overview of SNPs can be seen in Table 6.

Rapid virological response

An overview is presented in Table 7. Lagging *et al.*^[34] (2011) examined IP-10's ability to predict virological response and treatment outcome in 170 patients with genotype 1, from the DITTO-HCV study group. After six weeks, patients were randomized to individualized treatment,

or continued on the standard combination therapy as no sub analysis on SVR for patient receiving therapy, corresponding with the review's inclusion criteria for the course of 24-48 wk, was provided. Only results regarding RVR are featured in the review. The study found that patients obtaining RVR had significantly lower median baseline IP-10 levels than patients without a RVR. These findings were similar to results reported by Fattovich *et al.*^[21] that patients infected with HCV, genotype 1, who achieved RVR, had a significant lower mean baseline IP-10, than those who did not. However, this association was not seen for patients infected with HCV genotype 2 or 3. The study also enrolled genotype 4 infected patients, but due to insufficient numbers ($n = 15$), these were excluded. Al-Ashgar *et al.*^[19], 2013 studied the relationship between IP-10 and virological response in patients infected with genotype 4, and showed a trend

Table 1 Overview of the modified Delphi, 18-point quality assessment checklist for studies included in the review

Ref.	Yes response	No response	Partiel reported/unclear	Assessment
Fattovich <i>et al</i> ^[21]	16	2	0	High-quality
Diago <i>et al</i> ^[7]	15	2	1	High-quality
Apolinario <i>et al</i> ^[9]	14	2	2	High-quality
Darling <i>et al</i> ^[31]	14	1	3	High-quality
Lagging <i>et al</i> ^[34]	14	3	1	High-quality
Al-Ashgar ^[19]	13	3	2	Low-quality
Derbala <i>et al</i> ^[32]	13	2	3	Low-quality
Kurelac <i>et al</i> ^[33]	12	3	3	Low-quality

Studies was ranked as high quality if they provided ≥ 14 "yes" answers, or low quality if they provided ≤ 13 "yes" answers.

towards lower mean baseline IP-10 in patients with RVR, than in those without, though the association was not significant.

SVR

An overview is presented in Table 8. Following the pattern regarding RVR, all five studies examining SVR in relation to baseline IP-10 levels for HCV genotype 1 infected patients, showed a significant association.

Apolinario *et al*^[9] enrolled 63 Spanish patients from clinical trials and out patient clinics. Forty-three patients had genotype 1, while 20 had a non-1 genotype. Among the 43 HCV genotype 1 infected patients, mean baseline IP-10 levels were significantly lower in patients who reached a SVR compared to those who did not. Because some of the genotype non-1 infected patients received 48 wk of therapy, the results for these are not provided in Table 7. Diago *et al*^[7] also found a significant association between mean baseline IP-10 and SVR for their overall population of Spanish patients. An association that remained significant, when the analysis was restricted to HCV genotype 1 infected patients. The same significant association between lower baseline IP-10 and SVR for HCV genotype 1 infected, were reported for Italian, Croatian and American patients^[21,31,33]. An interesting aspect of the study by Kurelac *et al*^[33], 2012 was, that the greatest difference in IP-10, between patients with a SVR vs non-SVR, was seen at treatment week 4, where median IP-10 levels were 185 pg/mL (63-518) and 424 pg/mL (90-815) ($P < 0.0001$), respectively. Darling *et al*^[31] noted, that the significant association between baseline IP-10 levels and SVR remained when patients were grouped as Caucasian Americans (CA) or African Americans (AA) (447 ± 44 pg/mL vs 677 ± 69 pg/mL, $P < 0.001$ and 418 pg/mL ± 35 vs 716 pg/mL ± 55 , $P < 0.001$, respectively). Fattovich *et al*^[21] were the only ones that reported on HCV genotype 2 and 3 patients. As with the results regarding RVR, no association was found between SVR and baseline IP-10. Derbala *et al*^[32] and Al-Ashgar *et al*^[19] studied HCV genotype 4 infected Egyptian and Saudi patients, respectively, and showed significantly higher values of baseline IP-10 in non-SVRs

than in SVRs. Interestingly, a sub analysis, performed by Al-Ashgar *et al*^[19] on genotype 4a and 4d, showed that this correlation was present for genotype 4d (465.9 pg/mL ± 349.1 vs 904.9 pg/mL ± 532.1 , $P < 0.001$), but not for genotype 4a (564.7 pg/mL ± 288.9 vs 568 pg/mL ± 384.9 , $P = 0.300$). Derbala *et al*^[32] failed to provide information on the exact levels of IP-10, and instead provided a graphic depiction, which could not be interpreted to adequate results.

DISCUSSION

Several studies have independently shown levels of IP-10 to be associated with both RVR and SVR to peg-IFN/RBV treatment for CHC patients infected with HCV, genotype 1 and 4, but not for genotype 2 and 3. We conducted this systematic review to assess variation in IP-10's predictive ability for RVR and SVR to peg-INF/RBV treatment in patients chronically infected with HCV genotypes 1-4.

Our main findings indicate that a correlation exist between baseline IP-10 and SVR- and in part for RVR - for genotype 1 and possibly for genotype 4, however not for genotype 2 or 3.

Three studies provided information on baseline IP-10 in relation to RVR^[19,21,34]. Studies reporting on HCV, genotype 1 infected patients, found significant lower baseline IP-10 values in patients achieving RVR compared to those who did not^[21,34]. Only a trend, failing to reach significance, was described between baseline IP-10 and RVR in genotype 4 infected patients^[19] and no significant relation was found in relation to genotype 2 or -3^[21]. Seven studies provided information on baseline IP-10 in relation to SVR^[7,9,19,21,31-33]. All five studies reporting on HCV genotype 1 infected patients^[7,9,21,31,33] found significantly lower IP-10 levels of SVR than non-SVR. Diago *et al*^[7] did not provide separate results for the group of genotype non-1 patients included, which was surprising, as three quarters of the patients were infected with HCV, genotype 1, and could very well be the reason for finding a significant association in the overall population, when all genotypes were analyzed together. In line with this, Apolinario *et al*^[9] stated that no associations was found for their genotype non-1 group. However lacking differentiation into sub genotypes, compromise the value of information, especially as no association were found for HCV, genotype 2 or 3 infected^[21], and both studies reporting on genotype 4 infected patients^[19,32] found significant lower baseline IP-10 level in their populations, when comparing patients achieving SVR vs non-SVR. It should be noted, that while Fattovich *et al*^[21] considered two-sided P -values < 0.05 as statistical significant, only results of statistical tests with a P -value < 0.01 were considered of interest, because of the multiple comparisons between subjects with and without SVR. Therefore IP-10 was not considered to be associated with SVR, for HCV genotype 3 infected individuals, even though the p -value was found to be 0.02.

One study observed that the greatest difference in IP-10 levels was found at week 4. Patients, who at this

Table 2 Baseline total patient number, number of male patients, mean age, body mass index and ethnicity for the 8 included studies

Ref.	Patients		Mean age (yr)	BMI (kg/m ²)	Ethnicity		
	Males	Total (n)			Caucasian	African American	Asian
Apolinario <i>et al</i> ^[9]	40	63	41 (± 9.3) ⁵	Information not provided	Information not provided ⁶		
¹ Lagging <i>et al</i> ^[34]	169	252 ²			252 ⁹		
IL28B rs12979860 CC	64	93	41.6 (± 10.1) ⁵	25.1 (± 3.6) ⁵			
IL28B rs12979860 CT	77	123	41.9 (± 9.5) ⁵	25.0 (± 3.5) ⁵			
IL28B rs12979860 TT	28	36	41.9 (± 11.4) ⁵	25.0 (± 3.5) ⁵			
Diago <i>et al</i> ^[7]	77	137	42 (± 9.7) ⁵	Information not provided	Information not provided		
Fattovich <i>et al</i> ^[21]	133	226 ³	46 (± 11) ⁵	24.7 (± 3.8) ⁵	226		
Kurelac <i>et al</i> ^[33]	17	46	41.5 (± 12.4) ⁵	23.7 (21.9-25) ⁴	46		
Darling <i>et al</i> ^[31]	176	272	48.4 (± 7.4) ⁵	Information not provided	138	134	
Darbala <i>et al</i> ^[32]	144	159	46.47 (± 8.83) ⁵	30.18 (± 5.05) ⁵	Information not provided ⁷		
Al-Ashgar <i>et al</i> ^[19]	41	64	38.7 (± 11.5) ⁵	Information not provided	Information not provided ⁸		

¹Study did not provide baseline characteristics for their entire population, but instead provided baseline demographics in accordance with IL-28 genotype (only baseline characteristics for rs12979860 are reported in the review, as these were representative for the study population); ²253 was reported to be enrolled, however when adding the males and female patients, it sums to 252; ³Only 226 out of 280 patients had serum available for iP-10 testing; ⁴Median (25-75 percentiles); ⁵Mean (SD); ⁶51 patients from clinical trials had Spanish nationality; ⁷Egyptian nationality; ⁸Saudi nationality; ⁹95% of the original DITTO patient population were Caucasian. BMI: Body mass index.

Table 3 Hepatitis C virus-RNA and patient liver enzyme status for the 8 included studies

Ref.	HCV-RNA				All patients	Liver enzyme level	
	High viral load		Low viral load			AST	ALT
	<i>n</i>	Limit	<i>n</i>	Limit			
Apolinario <i>et al</i> ^[19]	28	≥ 6.3 log IU/mL ⁵	35	< 6.3 log IU/mL ⁵			118 IU/L (± 64) \$
¹ Lagging <i>et al</i> ^[34]							
IL28B <i>rs12979860 CC</i>					6.3 log IU/mL (± 0.8) ³	Information not provided	
IL28B <i>rs12979860 CT</i>					6.1 log IU/mL (± 0.7) ³		
IL28B <i>rs12979860 TT</i>					5.9 log IU/mL (± 0.8) ³		
Diago <i>et al</i> ^[7]	85	≥ 5.7 log IU/mL ⁵	52	< 5.7 log IU/mL ⁵			117.2 IU/L (± 81.6) ³
Fattovich <i>et al</i> ^[21]	147	≥ 5.6 log IU/mL ⁵			5.74 log IU/mL (± 0.9) ^{3,5}		92 IU/L (± 78) ³
Kurelac <i>et al</i> ^[33]					5.55 log IU/mL (5.52-6.1) ^{2,5}	Information not provided	
Darling <i>et al</i> ^[31]					6.66 log IU/mL (± 6.76) ^{3,5}		90.9 IU/L (72.9) ³
Darbala <i>et al</i> ^[32]					4.95 log IU/mL (3.6-5.63) ^{4,5}	38 IU/L (27-51) ⁴	51 IU/L (34-87) ⁴
Al-Ashgar <i>et al</i> ^[19]	45	≥ 5.78 log IU/mL	19	< 5.78 log IU/mL ⁵		67.5 IU/L (43.5-106.8) ²	56.0 IU/L (32.0-86.0) ²

¹Lagging *et al* provided baseline demographics in accordance with IL-28 genotype (only baseline characteristics for rs12979860 are reported in the review, as these were representative for the study population); ²Median (25-75 percentiles); ³Mean (SD); ⁴Median (IQR); ⁵Recalculated into log IU/mL. HCV-RNA is shown as number of patients with high or low viral load or as the mean or median for the entire population. Depending of the presentation in the original article, levels of ALT, AST or both are shown. HCV: Hepatitis C virus; ALT: Alanine transaminase; AST: Aspartate transaminase.

point had IP-10 levels higher than 250 pg/mL, had a 40-fold risk of not reaching SVR compared to patients with IP-10 levels lower than 250 pg/mL^[33]. This might indicate, that IP-10 levels at treatment week 4, could be used to assess if peg-INF/RBV treatment should be discontinued or not in genotype 1 patients - and perhaps could also be used to evaluate the need for adjacent DAA treatment (*i.e.*, using a 4 wk lead in phase with peg-INF/RBV treatment before apprising the need for DAAs). However, the small number of patients participating calls for caution when interpreting these results, and further studies of IP-10 levels at treatment week 4 should be encouraged.

One study^[31] showed that the correlation between baseline IP-10 and SVR remained significant even when the population was grouped according to ethnicity ($P < 0.001$). The latter is interesting as AA ethnicity is otherwise considered an unfavorable prognostic factor for obtaining SVR^[36-38], and might imply that IP-10 could help aid the

decision as to whom would have the greatest potential benefit from peg-INF/RBV treatment regardless of ethnicity. In this context it is interesting that it has previously been shown that HCV infected AA had higher IP-10 levels than corresponding CA patients, while uninfected AA had IP-10 levels similar to uninfected CA^[28]. The effect of race on Interferon Stimulated Genes, once at the stage of CHC, should therefore be examined further.

Findings, regarding SVR for HCV genotype 2 and 3, followed the same pattern as the results for RVR with no association between baseline IP-10 and SVR present for genotype 2 or 3^[21]. Supporting our findings, this lacking correlation in patients with HCV genotype 2 and 3, has also been shown when treating patients with standard and low (90 µg once weekly) peg-INF/RBV regimens^[22].

As mentioned, a significant correlation between IP-10 and SVR was reported by both studies, including HCV genotype 4 infected patients^[19,32]. One of these^[19] also performed differentiated analyses on HCV genotype 4

Table 4 Genotype and liver fibrosis stage for the 8 included studies

Ref.	Genotype (n)				Method	Liver fibrosis stage						
	1	2	3	4		0	1	2	3	4	5	6
Apolinario <i>et al</i> ^[9]	43	20			Scheuer score	28		35				
Lagging <i>et al</i> ^[34]	170 ¹	23 ¹	49 ¹	11 ¹	Ishak score	11	61	65	30	15	20	14
IL28B <i>rs12979860</i> CC	44	13	33	3		3	18	27	11	5	12	5
IL28B <i>rs12979860</i> CT	96	7	15	5		7	35	27	17	7	6	6
IL28B <i>rs12979860</i> TT	30	3	1	3		1	8	11	2	3	2	3
Diago <i>et al</i> ^[7]	103	9	25		Ishak score	106				31		
Fattovich <i>et al</i> ^[21]	92	87	47		Metavir ²	121			21			
Kurelac <i>et al</i> ^[33]	46				Ishak		34			12		
Darling <i>et al</i> ^[31]	272				Ishak	220				52		
Darbala <i>et al</i> ^[32]				159	Scheuer score		109		50			
Ashgar <i>et al</i> ^[19]				64	Metavir	34 ³			10 ³			

¹Baseline information for the sub analysis of IL28 12979860. Two hundred and fifty-two patients are reported to be enrolled, however adding the genotypes yields 253 patients. Likewise biopsies from 228 patients are described, however when adding the Ishak scores only yields 216 patients; ²Biopsies only available for 142 patients; ³Histology available for 44 patients; ⁴Lagging *et al* provided baseline demographics in accordance with IL-28 genotype (only baseline characteristics for rs12979860 are reported in the review, as these were representative for the study population). A box stretching over two - or more genotypes or fibrosis stage, indicates that the number refers to the combined group.

Table 5 Overview of the treatment regimens for pegylated interferon in combination with ribavirin, for the 8 studies included, in relation to dose and duration

Ref.	Genotype		Duration	Interferon treatment	Ribavirin treatment
Apolinario <i>et al</i> ^[9]	Multi-centerpatients	1	48 wk	180 µg peg-INF-α-2a once weekly	800 mg per day or 1000 mg < 75 kg, 1200 mg > 75 kg
		Non-1	24-48 wk		
	Out patiens	1	48 wk	peg-INF-α2b 1.5 µg/kg per week	1000-1200 mg per day
		Non-1	24 wk		
Lagging <i>et al</i> ^[34]	1		6 wk ¹	180 µg peg-INF-α-2a once weekly	1000 mg < 75 kg, 1200 mg > 75 kg per day
Diago <i>et al</i> ^[7]	1		48 wk	peg-INF-α-2b 1.5 µg/kg per week or 180 µg peg-INF-α-2a/week	1000 mg < 75 kg, 1200 mg > 75 kg per day
	Non-1		24 wk		
Fattovich <i>et al</i> ^[21]	1 and 4		48 wk	peg-INF-α-2b 1.5 µg/kg per week or 180 µg peg-INF-α-2a/week	800-1200 mg per day
	2 and 3		24 wk		
Kurelac <i>et al</i> ^[33]	1		48 wk	peg-INF-α-2b 1.5 µg/kg per week	Weight based ribavirin treatment ²
Darling <i>et al</i> ^[31]	1		48 wk	180 µg peg-INF-α-2a once weekly	1000-1200 mg per day
Derbala <i>et al</i> ^[32]	4		48 wk	Peg-IFN once weekly ³	1000 mg < 75 kg, 1200 mg > 75 kg per day
Al-Ashgar ^[19]	4		48 wk	180 µg peg-INF-α-2a once weekly	1000 mg < 75 kg, 1200 mg > 75 kg

¹After 6 wk, patients were randomized to differentiated treatment regimes; ²No further information on ribavirin treatment was provided; ³No further information on the subtype of peg-IFN was provided. Apolinario *et al*^[9] feature patients from both an outpatient clinic as well as patients from two multicenter trials receiving different treatment regimens, illustrated by the segregation in the genotype column. peg-IFN: Pegylated interferon.

subtypes, 4a and 4d, showing a significant association only for the latter ($P = 0.330$ and $P < 0.001$, respectively). It would have been interesting to examine if this was also the case for RVR, as it could be speculated that the association between baseline IP-10 and RVR in HCV genotype 4 infected patients failed to show significance, because both subtype 4a and 4d were analyzed as a whole. Therefore, subsequent studies making RVR and SVR assessments should be encouraged to perform differential analysis on individual viral subtypes, in order to uncover more specific associations. The setup for this study, did not allow us to investigate, what specific mechanisms account for the differences in correlation between baseline IP-10 and HCV genotype 1 and 4 compared with HCV genotype 2 and 3. However it is of great interest that these differences occur, and should be investigated further. Inversely patients infected with HCV genotype 2 or 3 generally has a more favorable response to treatment with PEG-IFN and RBV. Therefore, in a clinical setting the underlying mechanism

might not be relevant, as genotype 2 and 3 patients would readily be treated, whereas clinicians might be more reluctant to initiate peg-INF treatment to genotype 1 and 4 - infected individuals and here IP-10 levels might help to show which patients should undergo treatment.

This review focused on the association between pre-treatment IP-10 levels and virological responses. However, IL28B SNPs should be addressed when considering IP-10, as they are strongly linked with treatment response to Peg-INF/ RBV^[39-45]. Especially are homozygote genotypes at markers *rs8099917* (TT), *rs12979860* (CC) and *rs12980275* (AA) associated with a favorable outcome to treatment. While IL28B polymorphisms were not found to be predictive for treatment response in HCV genotype 2 and 3 infected individuals by Fattovich *et al*^[21], pretreatment IL28B polymorphisms, HCV-RNA- and IP-10 levels independently predict RVR in HCV genotype 1 infected individuals, with RVR in turn being the strongest predictor of SVR. Combining the IL28B polymorphisms and HCV-

Table 6 Overview of the marker distribution, in the four studied that supplied information on interleukin 28B single nucleotide polymorphism

Ref.	Genotype (n)	rs12979860			rs12980275			rs8099917			rs11881222		
		CC	CT	TT	AA	AG	GG	TT	TG	GG	AA	AG	GG
Lagging <i>et al</i> ^[30]	1 (253)	93	123	37	101	115	37	153	90	10			
Fattovich <i>et al</i> ^[21]	1 (92)	33	44	15	33	45	14	49	38	5			
	2 (87)	34	43	10	34	42	11	47	34	6			
	3 (47)	25	21	1	25	20	2	34	13	0			
Darling <i>et al</i> ^[31]	1 (201)	63	103	44									
Derbala <i>et al</i> ^[32]	4 (159)	57	77	25				96	55	8	64	75	20

Genotype column indicates specific genotype, and total number of patients with the specific genotype. Each marker column is divided into allelic distribution for the IL28B SNP genotype. SNP: Single nucleotide polymorphism.

Table 7 Overview of rapid virological response in the 3 studies providing information on baseline inducible protein-10's, and hepatitis C virus RNA levels at week 4

Ref.	Patients (n)	IP-10 measurement method	Genotype (n)	Baseline IP-10 concentration, grouped by rapid virological response (pg/mL)			Overall RVR (n)	
				RVR	Non-RVR	P-value	RVR	Non-RVR
Lagging <i>et al</i> ^[34]	170	ELISA (Quantikine, R and D systems, Minneapolis, MN, United States)	1 (170)	222	401	$P < 0.01$ (median)	33	137
¹ Fattovich <i>et al</i> ^[21]	226	ELISA (Quantikine, R and D systems, Minneapolis, MN, United States)	1 (92)	2.4 (± 0.28)	2.6 (± 0.25)	$P < 0.01$ (log mean \pm SD)	172	108
			2 (87)	2.38 (± 0.31)	2.3 (± 0.30)	$P > 0.05$ (log mean \pm SD)		
			3 (47)	2.45 (± 0.23)	2.48 (± 0.39)	$P > 0.05$ (log mean \pm SD)		
Al-Ashgar <i>et al</i> ^[19]	64	ELISA (Quantikine, R and D systems, Minneapolis, MN, United States)	4 (64)	483.9 (± 261.6)	609.9 (± 424.3)	$P > 0.05$ (mean \pm SD)	12	52

¹Entire patient population was 280, genotype 4 infected were removed from the analyses, and IP-10 results was available for 226 patients. IP-10: Inducible protein-10; RVR: Rapid virological response.

RNA yielded a specificity of 98% but a low sensitivity of 39%. By including IP-10 values in the equation, the sensitivity and the negative predictive value was raised from 81% to 94%, however lowering the positive predictive value from 87% to 76%. This is consistent with other findings in HCV genotype 1 infected, homozygous carriers of the favorable IL28B SNPs, with low IP-10 level, which also significantly predicted a first phase decline of HCV RNA, which translated into increased rates of RVR and SVR^[30]. While the two latter studies was carried out solely on Caucasian patients infected with HCV genotype 1, the additive predictive effect has also been shown for both HCV genotype 1 infected AA and CA patients^[31], and HCV genotype 4 infected patients^[32], respectively. Although low in numbers, these results could indicate, that both variables should be considered in a clinical context, before initiating treatment with Peg-INF/RBV in patients infected with HCV genotype 1 or 4. Further studies examining the association in HCV genotype 2 and 3 infected patients should be encouraged.

Conducting a systematic review with clear and stringent in- and exclusions criteria, is an obvious strength of this study, ensuring homogeneity between the studies included, hereby allowing an unbiased assessment of the current evidence. Another strength of our study was that we assessed the quality of the studies included, and provided a detailed declaration of the studies aim,

method - including treatment regimens and duration, as well as baseline patient demographics for the individual studies - supplying a solid ground for interpreting the results put forth. Although some authors recommend the use of quality assessments, other consider them misleading^[46], and there remains uncertainties about the relationship between methodology, validity and the use of sum scores to judge the quality of studies^[47]. Therefore we chose not to exclude any articles based on their quality score (e.g., high quality or low quality), but instead presented the ratings of the studies in the review to serve as an objective guide to interpret the review's results, rather than a tool for selecting studies for the review. As seen by the exclusion criteria, we wished to eliminate the possible uncertainties that could arise by including studies treating HIV/HCV - or HBV/HCV co-infected patients. Therefore, it should be mentioned that even though there was no indication towards inclusion of co-infected patients, three of the included studies, based in the United States, Croatia and Egypt, contained no clear exclusion criteria for HIV- or HBV- infection^[31-33].

Only a limited number of articles fulfilled the in- and exclusion criteria to be assessed in this review. Hence, more work is needed to establish a sufficient ground for final conclusions to be made. Further, there was an overweight of studies that addressed the association between SVR and baseline IP-10 in CHC patients infected

Table 8 Overview of sustained viral response in the 8 studies providing information on baseline inducible protein-10's, and hepatitis C virus-RNA levels 24 wk after end-of- treatment

Ref.	Patients (n)	IP-10 measurement method	Genotype (n)	Baseline IP-10 concentration, grouped by sustained virological response (pg/mL)			Overall SVR	
				SVR	Non-SVR	P-value	SVR	Non-SVR
Apolinario <i>et al</i> ^[9]	63	ELISA (OptEIA, Pharmingen, San Diego, CA, United States)	1 (43)	245 (± 154)	381 (± 138)	$P < 0.05$ (mean ± SD)	36	27
Diago <i>et al</i> ^[7]	137	ELISA (Human immunoassay kit; BioSource Europe SA, Nivelles, Belgium)	1 (103)	347 (± 197.4)	500.6 (± 311.2)	$P < 0.01$ (mean ± SD)	79 ²	58 ²
			1 (103)	332.4 (± 222.1)	476.8 (± 305.3)	$P < 0.01$ (mean ± SD)		
			2 (9)					
¹ Fattovich <i>et al</i> ^[21]	226	ELISA (Quantikine, R and D systems, Minneapolis, MN, United States)	1 (92)	2.47 ± 0.23	2.65 ± 0.28	$P < 0.001$ (log mean ± SD)	209 ²	71 ²
			2 (87)	2.37 ± 0.31	2.33 ± 0.35	$P > 0.05$ (log mean ± SD)		
			3 (47)	2.42 ± 0.21	2.67 ± 0.46	$P < 0.05^a$ (log mean ± SD)		
Kurelac <i>et al</i> ^[33]	46	ELISA (Quantikine, R and D systems, Minneapolis, MN, United States)	1 (46)	185 (63-518)	395.5 (111-926)	$P < 0.0001$ (median, range)	26	20
Darling <i>et al</i> ^[31]	272	ELISA (Quantikine, R and D systems, Minneapolis, MN, United States)	1 (272)	437 (± 31)	704 (± 44)	$P < 0.001$ (mean ± SD)	157	115
Derbala <i>et al</i> ^[32]	159	Luminex, Cytokine multiplex immunoassay kit (Merck Millipore, Billerica, MA, United States)	4 (159)	Exact data not provided, only graphic presentation		$P < 0.001$ (median, IQR)	98	61
Al-Ashgar <i>et al</i> ^[19]	64	ELISA (Quantikine, R and D systems, Minneapolis, MN, United States)	4 (64)	462 (± 282.6)	840.4 (± 490.6)	$P < 0.01$ (mean ± SD)	41	23

¹Entire patina population was 280, genotype 4 removed from the analyses, and IP-10 results was available for 226 patients Note that M. Derbala *et al* did not provide written specification on IP-10 levels for SVR compared to non-SVR, and only supplied a graphic depiction, which could not be interpreted to adequate results; ²SVR for the entire population. ^a $P = 0.02$. Only the results of statistical tests with a P value < 0.01 were considered of interest, because of the multiple comparisons between subjects with and without SVR. SVR: Sustained viral response; IP-10: Inducible protein-10.

with HCV genotype 1, whereas there was only a small fraction addressing the association between SVR and baseline IP-10 for genotype 2, 3 and 4, as well as studies examining the relationship between RVR and baseline IP-10 constituting an insufficient base for assessing baseline IP-10's predictive ability in these regards.

In this systematic review, we found correlations between baseline IP-10 levels and SVR in patients chronically infected with HCV genotype 1 and 4, while no such association was found for patients infected with HCV genotype 2 or 3. Likewise, we found indications of a possible correlation between baseline IP-10 and RVR for HCV genotype 1 infected patients, while no such association were found for HCV genotype 2 or 3 patients, and only a trend was found for HCV genotype 4 infected patients. However, the amount of information regarding baseline RVR for genotypes 1-4, and SVR's relation with baseline IP-10 for genotypes 2, 3 and 4 were insufficient for final conclusions.

COMMENTS

Background

Until recently, the standard of care for chronic hepatitis C (CHC) patients was lengthy dual therapy with pegylated interferon plus ribavirin (peg-IFN/RBV), a treatment with modest success rates, severe adverse events and variation in treatment response between hepatitis C virus (HCV) genotypes. Therefore, efforts to identifying biomarkers that can predict virological responses to treatment have been made. Interferon- γ inducible protein-10 (IP-10) is one such promising

marker, with several studies independently showing an association between virological response and baseline IP-10 concentrations for CHC patients infected with HCV genotype 1 and 4. However, the association seems to be lacking for CHC patients, infected with HCV genotype 2 and 3.

Research frontiers

IP-10 has been shown to be expressed at higher levels in HCV genotype 1 infected CHC patients with moderate to severe fibrosis compared to patients with mild or non fibrosis. Therefore, studies are being made to examine if this correlation is also found in HCV genotype 2 and 3 infected CHC patients. In addition to this, examinations of baseline IP-10 ability to predict fibrosis progression in CHC patients are pending. IP-10 research in relation to CHC is therefore expanding from the possible correlation between virological response to treatment with peg-IFN/RBV at baseline, to also include fibrosis score at baseline and fibrosis progress over time.

Innovations and breakthroughs

Despite the work done so far to correlate IP-10 levels to treatment response, this is to our knowledge, the first systematic review to address and clarify the differences in IP-10 properties, in relation to the different HCV genotypes and virological response. The authors found indications of correlations between baseline IP-10 levels and SVR in CHC patients infected with HCV genotype 1 and 4, but not in patients infected with HCV genotype 2 or 3. Likewise, the authors found indications of a possible correlation between baseline IP-10 and RVR for HCV genotype 1 infected patients, while no such association were found for HCV genotype 2 or 3 patients, and only a trend was found for HCV genotype 4 infected patients.

Applications

Despite of the great advantages with the new treatment options with direct acting antivirals (DAA), the cost of DAAs will without doubt substantially delay their introduction as standard treatment in low and middle-income countries by

years to come. In addition, DAA in high-income countries is still reserved for patients with advanced liver disease. Therefore, peg-IFN/RBV treatment still has a role to play in treatment of patients with CHC. Their findings of a possible correlation between baseline IP-10 levels and SVR in CHC patients infected with HCV genotype 1 and 4 but not for genotypes 2 and 3 could be beneficial in a clinical setting. Genotype 2 and 3 patients would readily be treated, as these patients generally have a favorable outcome to peg-IFN/RBV compared to genotype 1 and 4 infected individuals. In such patients, IP-10 levels might help to show which patients would have the best prognosis for a positive outcome to treatment.

Terminology

Interferon- γ inducible protein-10, more commonly denoted IP-10 or CXCL10, is a non-ELR-CXC chemokine, binding to the CXC-receptor-3. It functions as a chemotactic, attracting T lymphocytes and NK cells to the site of inflammation. Within the liver, IP-10 mRNA is produced by hepatocytes in inflammatory areas, and both intrahepatic IP-10 mRNA - and plasma levels of IP-10 are elevated in individuals with CHC, indicating that intrahepatic IP-10 is the source of plasma IP-10. The hypothesis therefore is that IP-10 can function as proxy for the level of liver inflammation, which in turns lead to fibrosis formation.

Peer-review

This is a well written and comprehensive systemic review to explore the association between baseline levels of interferon- γ -inducible protein-10 and virological response to treatment with pegylated interferon and ribavirin among patients chronically infected with hepatitis C virus, genotype 1-4.

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